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DEVICES FOR USE IN MEDICINE

FIELD OF THE INVENTION

This invention relates to an organ culture device for culturing a viable organ, in particular an organ consisting of or containing viable cells. The invention also relates to components which find application in the organ culture device of the invention and may find application in other uses, in particular a pump for liquid and a gas pressure control device for delivering a supply of pulsed pressurised air.

BACKGROUND OF THE INVENTION

By the term "viable organ" is here meant an organ of natural or synthetic origin which consists of or comprises living cells. The cells require culturing in order that at least they shall be maintained in a viable state and optionally grow. Such viable organs are used in medicine, in veterinary science and in other biological and biotechnical fields. The organ may be for example of natural origin, having been removed from a living creature for transplant or other purpose, or may be at least partially synthetic. For example a synthetic construct may have a synthetic substrate of biologically compatible material, on or in which cells are present. The organ may be in storage or may be undergoing culturing for the purposes of growth of the cells, for example in a synthetic construct where the cells are growing and adapting to mimic a natural organ. Our International Patent Application PCT/GB02/01183 filed 26 March 2002 and published as WO 02/077336 describes

synthetic viable organs containing cells and their manufacture.

Many methods and apparatus for maintaining cells in a viable state, for storage and/or growth, by maintaining and moving culture medium in contact with the cells are known.

SUMMARY OF THE INVENTION

The present inventors have realised that there is a need for a simple organ culture device for culturing a viable organ, which is easily maintained during storage and/or transport.

The viable organ employed in this invention may be in the form of a sheet or a tube or it may be a hollow organ and typically comprises a sheet, tube or hollow structure containing or consisting of conjoined cells and extracellular matrix, together with preferably a layer of endothelial cells on at least one surface thereof. The cells joined by extracellular matrix are typically smooth muscle cells or fibroblasts. Examples are:

sheet:

skin construct: sheet of fibroblasts and extracellular matrix (ECM), with an epithelial cell layer

hollow organ (in the form of tube):

bladder: smooth muscle/ECM tube + transitional epithelium

stomach: smooth muscle/ECM + specialised gastric type epithelium

tube

portion of gut (e.g. oesophagus, small intestine, colon, rectum):

oesophagus - smooth muscle/ECM +squamous epithelium

small intestine/colon/rectum - smooth muscle/ECM + columnar epithelium + goblet cells

blood vessel or arterio-venous shunt: smooth muscle cells/ECM with endothelial cell layer

urethra or ureter: smooth muscle/ECM with transitional cell layer

The viable organ may, for example, by an artificial surgically implantable construct containing living cells.

The production of artificial constructs in the form of sheets or tubes, possibly containing living cells, is described in our co-pending International Patent Application having the title "Methods and Apparatus for Forming Hardened Tubes and Sheets", filed on 26 March 2002 and published as WO 02/077336 and also in our co-pending UK Patent Application 0301834.8 filed 27 January 2003. A delivery assembly for delivering such a construct or organ is described in our co-pending International Patent Application having the title "Delivery Assembly for Use in Surgery", claiming priority from UK Patent Application No. 0207416.9. The content of these Patent Applications is incorporated herein by reference.

In the organ such as a construct which is to be a portion of the gut, e.g. oesophagus, stomach, small intestine, colon or rectum, the smooth muscle cell tube

may desirably have a multiple layer structure, e.g. double or triple layer. A method of forming such a multiple layer is disclosed in WO 02/077336.

According to the invention in one aspect there is provided an organ culture device for culturing a viable organ, having a chamber for containing the viable organ, located along a liquid flow path for a flow of culture medium through the chamber; and a pump provided along the liquid flow path, for pumping the culture medium, wherein the pump has a pump chamber with a net flow direction for culture medium through the pump chamber, a pulsatile pumping action being obtainable by repeated deformation of a deformable wall of the pump chamber, disposed laterally of the net flow direction.

The pulsatile pumping action of the pump allows the developments of advantageous conditions in the chamber housing the organ. In particular, pulsed culture medium is believed to assist in the maintenance and development of some forms of tissue by mimicking conditions in the body. For example, if the tissue being cultured is blood vessel tissue, then a pulsed culture medium is believed to assist in the culture of a suitable endothelial cell layer.

The lateral disposition of the deformable wall with respect to the net flow direction of culture medium through the pump chamber allows deformation of the wall in a direction substantially transverse to the net flow direction.

The disposition of the deformable wall is advantageous because the flow characteristics of the pump, and hence the flow characteristics in the chamber in which the organ is located, may be improved in

comparison with alternate pump configurations. In particular, the turbulence of the flow can be reduced in comparison with a pump having equivalent stroke volume and stroke rate but with a deformable wall disposed in an alternative position, e.g. facing towards or away from the net flow direction.

Preferably, the deformable wall is a resiliently deformable wall. The wall is deformed by an external force, e.g. by pressure acting on its external surface. Once this pressure is removed, the resilience of the wall causes the wall to take up its non-deformed shape. This assists the flow of culture medium into the pump chamber for pumping in a subsequent stroke of the pump.

In this device, the liquid flow path provides for flow or circulation of the culture medium over surfaces of the viable organ. Preferably, the device also provides for gas transfer via gas transfer means between the exterior and the circulating culture medium, for example transfer of oxygen and if required carbon dioxide into the culture medium, or removal of carbon dioxide.

Preferably the gas transfer means operates by diffusion of gas through a gas-permeable wall. Typically, the device includes a conduit forming part of the liquid flow path. The device may therefore include a gas transfer chamber, having a wall which is a gas-permeable wall of the conduit, for containing the gas to be diffused through the gas-permeable wall.

Preferably the pump of the organ culture device is operated by pressurised gas. This is advantageous where it is desirable that the organ culture device requires no electrical power, for example during transport of the viable organ between hospitals. A simple gas-powered

pump is described below.

A gas powered pump can be cheaper and is more easily disposed of than an electrically powered pump. Disposability is a significant factor, if the organ culture device must be used only once (in order to avoid risk of cross-contamination between patients).

In the pump, the pumping action is preferably obtained by repeated deformation of the wall by pressurised gas outside the wall. The pressurised gas may be also the gas which effects gas transfer with the culture medium, and most preferably the resiliently deformable wall of the pump is itself gas-permeable, so that the gas transfer takes place through it. By combining the pumping action and the gas exchange action, a simple, economical and easily disposable device can be obtained.

In an alternative possible embodiment, the pressurised gas which operates the pump may conduct the gas exchange at a separate chamber in the culture medium circuit.

Typically, the pump has an inlet and an outlet at opposing ends of the pump chamber. These may be located on a longitudinal axis of the pump chamber. Preferably, the deformable wall is disposed between the inlet and outlet and substantially parallel to the longitudinal axis.

Preferably, the wall deforms inwardly towards the longitudinal axis of the pump chamber. It is not preferred that the deformation of the wall travels along the wall parallel to the longitudinal axis of the pump chamber, although such peristaltic pumping action might be possible.

Preferably, the resiliently deformable wall includes first and second portions. Alternatively, there may be first and second resiliently deformable walls of the pump chamber. Preferably, these first and second portions, or first and second walls, face or obliquely face one another laterally across the pump chamber. Thus, these elements are able to provide pumping action on the liquid contained in the pump chamber from different directions. This allows more efficient pumping by reducing the "dead" volume in the pump chamber, i.e. by reducing that volume of liquid which remains substantially stationary in the pump chamber even after repeated strokes of the pump.

More preferably, the resiliently deformable wall extends substantially circumferentially around the pump chamber. In this way, different portions of the deformable wall are deformable substantially towards the longitudinal axis of the pump chamber (which is aligned with the net flow direction). Typically, the deformable wall is a deformable tube. Such a construction allows reduction of the "dead" volume in the pump chamber for the same reasons as described above.

A tubular shape for the pump chamber, with the inlet and outlet located at opposing ends, allows pumping to be carried out at reduced turbulence. In particular, if the pump chamber (and preferably the deformable wall) is long in comparison to its width, it is possible for a satisfactory stroke volume of the pump to be displaced by only a relatively small deformation of the wall. This can assist in keeping turbulent flow to a minimum.

The device may include a reservoir for supplying culture medium to be pumped towards the chamber. The

liquid flow path, or a part of it, may extend from the reservoir towards the pump and optionally through the pump chamber.

The flow path may be non-circulatory. If the flow path is completely non-circulatory, then none of the culture medium is recirculated. In that case, the culture medium in the pump chamber comes only from the reservoir. For non-circulatory flow paths, culture medium collection means, e.g. a bag, is disposed downstream of the chamber. Preferably, the collection means and the chamber are in communication via a flow restrictor which can allow the build-up of back pressure in the chamber so that the organ can more easily be subjected to pulsatile flow from the pump.

Alternatively, the flow path may be circulatory, or partially circulatory. In that case, at least some of the culture medium is recirculated from the chamber back to the pump for pumping back to the chamber. The culture medium may be refreshed (e.g. intermittently or continuously) from the reservoir, if present. In that case, culture medium collection means is required to accommodate the overspill volume of culture medium in the flow path.

Preferably, the device includes sampling ports for sampling culture medium from the flow path, e.g. for analysis during use of the device.

For non-circulatory and for circulatory devices, it is preferred that the device is sealed liquid-tight, i.e. that culture medium from the reservoir or in the device is not exposed to the outside world. This helps to reduce the risk of infection or contamination of the culture medium and organ.

The whole of the organ culture device of the invention may be made of material which is suitable for irradiation in order to sterilise it, after its manufacture and assembly, for example using gamma-ray radiation.

In a second aspect, the invention provides a pump for liquid, suitable for use in the organ culture device of the invention described above, but also having other possible uses.

In this aspect, the invention provides a pump for liquid having a pumping chamber for the liquid, there being a net flow direction in the pumping chamber for pumped liquid; and a pumping member for acting on the liquid in the form of a deformable wall of the pump chamber, disposed laterally of the net flow direction, wherein the deformable wall is acted on by pulses of pressurised gas to cause pumping.

Such a pump is particularly useful and effective where relatively small quantities of liquid are to be handled. Thus the pumping chamber of the pump may have a volume of not more than 1 litre, or 100 ml or less, or even 10 ml or less. The volume of the pumping chamber is the volume between inlet and outlet directional flow devices which are typically provided in the pump, for example one-way valves.

The pump according to the invention may comprise means for generating a pulsed pressurised gas from a source of pressurised gas such as a reservoir, e.g. a gas cylinder. A suitable device for generating such a pulsed flow of pressurised gas is described below.

Preferred features of the pump are described in relation to the pump in the first aspect of the

invention, above. Preferred features described below may be incorporated with the first or third aspects of the invention.

The deformable wall portion of the pumping chamber is preferably resiliently deformable. It may be a tube containing the pumped liquid in use. This provides a simple construction of the device. In order to achieve gas transfer to and/or from the liquid undergoing pumping, the deformable wall portion may be gas-permeable. In this way for example, transfer of a gas such as oxygen into the liquid undergoing pumping may be achieved, where oxygenation is required. The pulsing of the pressure of the gas acting on the deformable wall portion improves the rate of gas transfer, by generating movement of the gas.

The pump of the invention may find application in other medical or veterinary uses and apparatus, and the invention extends to such uses. The pump being simple and not requiring electrical power may be used for example to pump blood, in a cardiac assist technique, providing an extra-corporeal cardiac assist. Where oxygen transfer takes place within the pump, the pump can effect oxygenation of the blood simultaneously.

According to the invention in a third aspect there is provided a gas pressure control device for delivering pulsed pressurised gas, comprising a gas accumulator chamber having an inlet for connection to a source of pressurised gas and an outlet, the gas accumulator chamber being resiliently expansible by movement of a movable wall thereof, the device having a valve member movable between a closed position closing said outlet and an open position permitting outflow through said outlet,

the device further having means actuated by the movement of the movable wall of the accumulator chamber to move the valve member from the closed position to the open position when a predetermined pressure is reached in the accumulator chamber and means for returning the valve member to the closed position upon contraction of the accumulator chamber following release of a volume of gas therefrom.

This device is self-cycling, and may require no external control, i.e. no external power source other than the supplied pressurised gas.

The resiliently expansible accumulator chamber may be a piston and cylinder assembly, the piston providing the movable wall of the chamber. The piston may carry an actuating member which initiates movement of the valve member away from its closed position. The device may include biasing means, operating on the valve member during its movement from its closed position, whereby after removal of the pressure differential across the valve member upon its opening the valve member is moved by the biasing means to its open position. The biasing means may be an element acting in tension between the movable wall of the accumulator chamber and the valve member and arranged to bias the valve member towards its open position during the opening of the valve member.

While this gas pressure control device finds particular application in controlling the gas pump described above, it may find other applications in medicine, and the invention extends to use of such a device in medicine and veterinary science processes and apparatus. The device may find use in delivering pulsed gas to a patient, for example in a positive pressure

ventilation system where a patient is fed pulsed air by the mouth or nose.

The invention further provides an organ culture device as described herein in a form ready for receiving a viable organ, e.g. by manufacture of the viable organ in the culture device, the device being sterilized in readiness for housing a viable organ and contained within a sealed enclosure maintaining its sterilized state.

The invention further provides a method of maintaining a viable organ for transport and storage, using an organ culture device of the first aspect.

INTRODUCTION OF THE DRAWINGS

Embodiments of the invention will now be described by way of non-limiting example, with reference to the accompanying drawings. In the drawings:-

Fig. 1 is a schematic part sectional diagrammatic view of an organ culture device according to a first embodiment of the invention.

Fig. 2 is a schematic part sectional diagrammatic view of an organ culture device according to a second embodiment of the invention.

Fig. 3 is a schematic part sectional diagrammatic view of an organ culture device according to a third embodiment of the invention.

Fig. 4 is a schematic sectional view of a pump, which is an embodiment of the invention and is employed in the organ culture device of Fig. 1, 2 and/or 3.

Fig. 5 is a schematic sectional view of the pump of Fig. 4, in a different phase of its operation.

Fig. 6 is a schematic sectional view of a pressurised gas flow control device, which is an

embodiment of the invention and is used in the organ culture device of Fig. 1, 2 and/or 3.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the drawings, the same reference numbers are used for the same or corresponding parts.

The organ culture device embodying the invention shown in Fig. 1 has a viable organ in the form of a tube 1 comprising living cells embedded in a matrix of sodium alginate hardened by contact with calcium chloride solution, housed in a cylindrical chamber or cavity 8 within a housing 2. The nature of this tube 1 and the housing 2, and the method by which the tube 1 is formed *in situ* in the housing 2 is described in more detail in our International Patent Application PCT/GB02/01183 (WO 02/077336) filed 26 March 2002, the contents of which are herein incorporated by reference.

Modifications of the embodiment of Fig. 1 are shown in Figs. 2 and 3. Common features are described below.

The housing 2 shown in Fig. 1 has a main body part 13 which is a rectangular block having a central recess 13a whose face lies at the section line in Fig. 1, this face having a semi-circular groove 14 which forms half the cylindrical cavity 8 containing the tube 1. The housing 2 has a second body part, not seen in Fig. 1, which fits sealingly into the recess 13a of the body part 13 and has a corresponding groove to form the other half of the cylindrical cavity 8 containing the tube 1. This cylindrical cavity extends into bores in the larger end portions 15, 16 of the main body part 13. The second body part is in place on the main body part 13 during the

manufacture of the tube 1 and remains in place during the culturing of the tube 1 as described below, being intended to be removed only by the surgeon during an operation on a patient, when the surgeon wishes to use the cultured tube 1.

To manufacture the tube 1 *in situ* in the housing 2, a slider member 18 (seen in its final position in Fig. 1) is initially present at the lower end of the cavity 14, seated on the sleeve 21. The slider 18 has a recess in its lower end in which the narrow tube 22 at the upper end of the sleeve 21 is located.

The sleeve 21, which is sealed by O-rings (not shown) to the cavity 14 within the end portion 16 of the body 13, is carried by a block 25 so that it can be moved upwardly into the position shown in Fig. 1, from a lower position in which the slider 18 is below the level of a side passage 20.

Sodium alginate solution containing living cells (which may be cells extracted from the patient into whom later the tube 1 is to be inserted surgically) is injected through the side passage 20 (e.g. from one of the ports 23,24 described below) so as to fill the cavity 14. Then the block 25 and the sleeve 21 carrying the slider 18 is pushed upwardly to the position shown in Fig. 1. Calcium chloride solution is injected through the conduit 28 into the interior of the sleeve 21 and emerges from the tube 22, driving the slider member 18, which acts as a regulator, upwardly along the cavity 14. The slider member 18 has an external diameter smaller than the internal diameter of the cavity 14, so that as it moves a thin layer of alginate is left behind it, which immediately contacts the calcium chloride solution

and is chemically hardened sufficiently to become a shaped body (this shaped body, which is the tube 1, is not rigid). The shaped body thus consists of a matrix of hardened alginate containing the viable cells. The slider member comes to rest, as shown in Fig. 1, beyond the junction with a side passage 11. During the movement of the slider 18, excess alginate solution emerges via the cap 12.

In the block portion 25 the conduit 28 joins a side tube 26 which ends at a connector 27. Before or after the formation of the tube 1, the side passage 11 and the side tube 26 are connected by a continuous conduit 9 to form a complete closed and sealed circuit including the cylindrical cavity 14 containing the tube 1. To maintain the sealed and closed nature of this circuit, the end cap 12, the side passage 20 and the conduit 28 must be kept closed. In Fig. 1, the conduit 9 has inlet and outlet ports 23,24 with valves, which permit the simultaneous injection and removal of liquid from the closed circuit, as required in order to change or refresh the liquid of the circuit. By this means, the circuit is washed to remove the alginate solution and calcium chloride solution, and then a culture medium of a suitable nature for maintaining and promoting growth of the cells in the tube 1 is added. Suitable culture media for this purpose are known in the art, and need not be described here.

The embodiment of Fig. 1 uses a fully recirculating liquid flow path, i.e. a closed circuit. In contrast, the embodiment of Fig. 2 uses a non-recirculating liquid flow path. In Fig. 2, culture medium reservoir 70 is attached, via tubing and a flow

restrictor 72, upstream of pump 3 in the liquid flow path. Culture medium flows into pump 3 by gravity flow. Flow restrictor 72 may be variable to allow different rates of flow from reservoir 70 into pump 3, depending on the rate of flow of culture medium required through cavity 14.

The culture medium flows from pump 3, through cavity 14 and downstream to side passage 11. A culture medium collection vessel 74 is connected to side passage 11 via flow restrictor 76. Culture medium which flows along side passage 11 drains into vessel 74 which may, for example, be a bag. Note that Fig. 2 is schematic and vessel 74 may be disposed lower than reservoir 70 to allow a hydrostatic head from the height difference to drive, in part, the flow of culture medium.

Flow restrictor 76 allows back pressure to build up in cavity 14 and throughout the flow path in general. Thus, a pulsatile pumping action by pump 3 allows pressure waves to be conducted along the flow path. Such pressure waves are believed to be of assistance in cell culture and growth.

The embodiment of Fig. 3 shows a device allowing partial recirculation of culture medium. A liquid flow circuit is definable in the sense that there is a liquid flow path from pump 3, through conduit 9, cavity 14 and back along side passage 11 to pump 3 again. However, a culture medium reservoir 80 is provided, communicating with conduit 9 via flow restrictor 82. Culture medium reservoir 80 is able to communicate downstream of pump 3 because sufficient culture medium is recirculated to allow pump 3 to operate satisfactorily.

Downstream of cavity 14 is provided a culture

medium collecting vessel 84. This communicates with side passage 11 via flow restrictor 86. In operation, vessel 84 collects the same volume of culture medium as dispensed into the flow circuit from reservoir 80, because the flow circuit requires a constant volume of culture medium.

Again, vessel 84 may be located at a lower height than reservoir 80, to allow gravity flow of culture medium along the flow path.

Sampling ports may be provided, e.g. in passage 88, for sampling used culture medium for analysis. Similarly sampling or injection ports may be provided, e.g. in passage 90, for sampling, diluting or adding to the culture medium in reservoir 80.

The flow path formed by the cavity 14 and the conduit 9 includes a pump 3 shown in detail in Figs. 4 and 5. The pump 3 is gas-operated, using gas from a compressed gas cylinder 5 supplied via an adjustable valve 7 and a pipe 6 to a control device 4 for providing pulsed pressurised gas to the pump 3. The control device 4 is shown in detail in Fig. 6.

By means of the pump 3, which requires no mechanical or electrical power, the culture medium is flowed along the flow path, so that the culture medium passes over at least the internal surface of the tube 1 (in practice, the tube 1 may separate from the wall of the cavity 14, so that the culture medium passes over both its surfaces). The flow of the culture medium is to some extent pulsed, since the pump 3 operates in a pulsation manner, which is believed to be advantageous for the culturing of the cells in the tube 1, if those cells in the natural state are accustomed to a pulsed

flow.

The pump 3 shown in Figs. 4 and 5 has a rigid composite body 30 consisting of two end members 31, 32 of moulded synthetic plastics material, each having a connection portion 33, 34 for sealed connection to the adjacent part of the conduit 9 and each containing a one-way valve. The one way valve has a valve seat 35 and a valve member in the form of a ball 36 and biased against the valve seat by a compression spring 37. These valves therefore permit unidirectional flow through the pump 3 in the direction of the arrow 38.

Connecting the two end members 31, 32 is a rigid cylindrical body part 39 also moulded in plastics material and having an inlet 40 and an outlet 41 for the pressurised driving gas. Within the body part 39 and sealed to the end body members 31, 32 is a cylindrical silicone rubber tube 42 having at its axial centre region a circumference recess 43 in its outer surface. The recess 43 provides a circumferential chamber extending around the tube 42 and communicating with both the inlet 40 and the outlet 41. The tube 42 at its central region thus has a thin wall portion 44 which is resiliently deformable and is much more easily deformed than the remainder of the tube 42. The outlet 41 includes a bleed orifice (not shown), to restrict the rate of flow of gas from the chamber 43.

The pump shown in Fig. 4 is operated solely by a pulsed supply of pressurised gas applied to the inlet 40, and produced in a manner to be described below. Each pressure pulse in the chamber 43 causes the thin wall portion 44 to be deformed resiliently inwardly as shown in Fig 5. This pushes a portion of the liquid contained

in the valve chamber 45 through the one-way valve 35, 36, 37 at the right-hand side of the pump as seen in Figs. 4 and 5. As the pressure pulse declines, by leakage from the outlet 41, the thin wall portion 44 returns to its cylindrical state, drawing a volume of the liquid into the chamber 45 through the one-way valve at the left-hand end of the pump.

The volume pumped by each "stroke", i.e. each pressure pulse, can be varied by varying the dimensions of the thin wall portion 44, and also by varying the pressure variation during the pressure pulse. The pumping rate can also be varied by changing the rate of the pressure pulses.

Any suitable gas may be used to power the pump, and no mechanical or electrical power source is required. Apart from the springs 37, the whole pump can be made of synthetic plastics material, and is therefore suitable for sterilisation e.g. by gamma-ray radiation.

In a modification of the pump, a rigid cylinder of plastics material having many apertures in its wall is inserted into the cavity 43 and presses on the end walls of the cavity 43 so that the thin wall portion 44 is maintained in a tensioned condition. This improves the resiliency of the wall portion 44 and its return to the cylindrical condition.

The silicone rubber tubing material used for the tube 42 is a conventional tubing material (AltiSil silicone tube of Altec, Bude, Cornwall, England) and has been found to be permeable by gases, due to gaseous diffusion. This permits diffusion of gas to or from the liquid in the pumping chamber 45. In particular, if the pumping gas used to drive the pump is or contains oxygen

and/or carbon dioxide, it is possible to pass oxygen and/or carbon dioxide into the liquid in the chamber 45. In this way, when the pump is in use in the organ culture device of Fig. 1, Fig. 2 or Fig. 3 there can be achieved in a simple and convenient manner the necessary exchange of oxygen and carbon dioxide with the flowing culture medium. Alternatively, a separate gaseous diffusion device can be provided in the flow path, for example another portion of gas permeable silicone tube. The gas employed in the separate gas diffusion device may be the gas actually used for driving the pump of Figs. 4 and 5.

To drive the pump, it is necessary to provide a pulsed supply of pressurized gas. In the device of Figs. 1, 2 and 3, this is achieved by a control device 4, shown in Fig. 6. Like the pump of Figs. 4 and 5, this device is powered solely by the pressured gas supplied to it and requires no other external power.

The device of Fig. 6 has a cylindrical body 50 with a peripheral gas inlet 51 and an axial outlet 52 in the end wall 53. A piston 54 is slidable axially along the cylinder 50 and sealed to the cylinder by O-rings 55. The piston 54 carries a rod 56 extending through an aperture in the second end wall 57 to stabilise the piston 54. This aperture and rod 56 are shaped to allow gas to pass in and out of the space on the left-hand side of the piston 54 as seen in Fig. 6. In this space is a compression spring 58 which biases the piston 54 towards the end wall 53.

On its front face, the piston 54 carries an axially projecting sleeve 59 having a central bore open at its front end and a closed-end slot 60 providing lateral access to the bore. Within this bore slides a

rod 61 which has a pin 62 projecting into the slot 60 and carrying at its forward end a valve member 63 having an O-ring 64 and sealing against a valve seat 65 around the entrance to the outlet 52. Surrounding the rod 61 is a coil spring 66 which is connected to the valve member 63 and to the sleeve 59 and is capable of acting as a tension spring when extended and as a compression spring when in a compressed state.

The device 4 operates as follows. Gas supplied at the inlet 51 under pressure drives the piston 54 to the left, against the action of the compression spring 58, in order to charge the cylinder chamber 67 to the right-hand side of the piston 54 with compressed gas. The valve member 63 is held against the valve seat 65 by the gas pressure differential across it. The pin 62 therefore slides along the slot 60 and the spring 66 is extended, but the tension force applied by the spring 66 is not sufficient to lift the valve member 63 from the seat 65. When the pin 62 reaches the right-hand end of the slot 60, the sleeve 59 pulls the rod 61 so that the valve member 63 is now lifted from the valve seat 65. The pressure differential across the valve member 63 thereby disappears, so that the spring 66 now pulls the valve member 63 and rod 61 rapidly to the left, opening the outlet 52 fully to allow delivery of a pulse of compressed gas from the device.

The pressure drop within the chamber 67 allows the compression spring 58 to drive the piston 54 to the right, carrying the valve member 63 back into contact with the seat 65, this contact being ensured by the pin 62 reaching the left-hand end of the slot 60. The spring 66 is designed so that the pin 62 is at a central region

of the slot 60, in the equilibrium position.

The cycle of charging the chamber 67 and release of the gas through the outlet 52 is then repeated.

The rate of outflow of gas through the outlet 52 when open must be greater than the inflow rate through the inlet 51. This can be achieved by a suitable bleed orifice or by adjustment of the control of valve 7 shown in Figs. 1, 2 and 3. The pressure differential across the device 4 may also control its stroke rate. The stroke rate and stroke volume can be adjusted by variation of the characteristics of the springs 58 and 66 and also the length of the rod 61.

Apart from the spring 66, the whole device shown in Fig. 6 can be made of gamma-ray sterilisable synthetic plastics material.

Though shown as a separate unit, the device 4 of Fig. 6 maybe incorporated in the structure of the pump 3, providing a unitary pumping device. One or both of these devices can also be incorporated with the body 2, to provide a unitary construction.

As described, the components 2, 3, 4 require no external power source, other than the source of pressurised gas, and furthermore are suitable for sterilisation. The assembly of components, e.g. the body 2, conduit 9 and pump 3, and optionally also the valve 4, may be inserted into a sterilisable packaging enclosure, of the type used for many surgical devices, which is then sealed. Suitable packaging material is Rexam Medical Packaging Integra (Registered Trademark) Form medical thermal-forming film. The device inside the sealed package may then be sterilised, for example by gamma radiation, in a known manner. In this form, it is

conveniently stored and transported when it is to be used to a laboratory for the initial stage of preparation of the viable organ, such as the tube 1. After formation of the tube 1, the device is ready immediately to commence the culturing stage by circulation of culture medium through the closed circuit, without requiring attachment of liquid lines and other devices. Contamination can be easily avoided throughout the duration of the culturing of the organ, which may require a period of many weeks.

The use of the pressurised gas for the powering of the device, this gas being sealed from the circulating culture medium, is convenient, since the consumption of the gas is relatively small, and is easily provided by a canister or cylinder of appropriate compressed gas. The filling state of such a cylinder or canister is easily monitored, by means of a pressure gauge. Electrically powered devices, which do not lend themselves easily to sterilisation and are relatively expensive, are avoided. When the organ culture device is being transported, for example between hospitals, it is convenient that no electrical power source is required.

Apart from the cylinder or canister of pressurised gas, the organ culture devices shown in Figs. 1 to 6 can be made almost entirely of parts which are made of synthetic plastics material, by injection moulding. The device is therefore cheap to manufacture, which is advantageous when the device is to be used only once. The device also meets the regulatory standard being set at present for disposability of medical devices.

While the drawings show an organ culture device which contains a viable organ in the form of a tube which is made <u>in situ</u> in the device, the present invention is

not restricted to this. The principle of operation of the device can be applied to the storage and transport of other viable organs, including organs of natural origin such as a kidney or blood vessel.

As discussed above, the pumps shown in Figs 4 and 5 and the control device for producing the pulsed pressured gas of Fig. 6 are capable of use in many other medical apparatuses and in devices and for purposes outside the medical field.